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| EXAMINER | |
|---|---|
| XIE, XIAOZHEN | |
| **ART UNIT** | **PAPER NUMBER** |
| 1646 | |

DATE MAILED: 12/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/737,208 | GILLIES ET AL. | |
| | Examiner | Art Unit | |
| | Xiaozhen Xie | 1646 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *23 September 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-11,14,15,17-24 and 27-48* is/are pending in the application.

4a) Of the above claim(s) *14,15,20-22 and 27-44* is/are withdrawn from consideration.

5)☒ Claim(s) *1-5* is/are allowed.

6)☒ Claim(s) *6-11,17-19,23,24 and 45-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## RESPONSE TO AMENDMENT

### *Status of Application, Amendments, And/Or Claims*

The Art Unit location and examiner of your application in the USPTO have changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1646, Examiner: Xiaozhen Xie.

Applicant's amendment of the claims and the specification has been received on 23 September 2005. Applicant's amendment of the Inventorship filed 28 October 2005 is acknowledged, and the inventorship in this nonprovisional application has been changed.

Claims 1-11, 14-24 and 27-44 are pending. Claim 16 has been cancelled and claims 14, 15, 20-22 and 27-44 are withdrawn. New claims 45-48 are added. Claims 1-11, 17-19, 23-24 and 45-48 are under examination in this office action.

### *Claim Rejections Withdrawn*

The Objection of the drawings is withdrawn in response to Applicant's argument and the agreement during the telephonic interview on 1 August 2005.

The Objection of the abstract of the disclosure is withdrawn in response to Applicant's amendment to delete the number "2722168".

The rejection of claims 1-11, 16-19, and 23-24 under 35 U.S.C. 112, first paragraph, as lacking written description is withdrawn in response to Applicant's amendment.

The rejection of claims 1-11 and 16-19 under 35 U.S.C. 102(b) as anticipated by Lode et al., (J. Clin. Invest., 2000, 105(11):1623-1630), and under 35 U.S.C. 102(e) as anticipated by Gillies et al. (U.S. Publication No. 20030166877) et al. are withdrawn in response to Applicant's amendment of the claims.

The rejection of claims 23-24 under 35 U.S.C. 103(a) as unpatentable over Lode et al. in view of Gillies et al. (WO 01/10912 A1) is withdrawn in response to Applicant's amendment of the claims.

***Specification***

The amendment of the specification filed 23 September 2005 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: on page 7, paragraph [00029], Applicant amended the specification to include "a $V_H$ region having at least one humanized FR, such as hu$V_H$FR1 or hu$V_H$FR3", while the original specification only discloses "a $V_H$ region having at least one humanized FR, such as hu$V_H$FR1 or hu$V_H$FR2". The amendment introduced new matter. Further, Obviousness is not the standard for the addition new limitations to the disclosure as filed. It cannot be said that a subgenus is necessarily described by a

genus encompassing it and a species upon which it reads. In re Smith 173 USPQ 679, 683 (CCPA 1972). See MPEP 2163.05(b). Therefore, the amendment of the specification to replacing $huV_HFR2$ with $huV_HFR3$ is not entered.

Applicant is required to cancel the new matter in the reply to this Office Action.

***Rejections maintained/New ground rejections***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 45 is rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the art that the inventor(s) had possession of the claimed invention at the time the application was filed.

The specification as originally filed does not provide support for the invention as now claimed: "The antibody variable region of claim 1 further comprising an amino acid sequence selected from the group consisting of amino acids 1-25 of SEQ ID NO: 2 and amino acids 67-98 of SEQ ID NO: 2".

Applicant's amendment, filed 23 September 2005, asserts that no new matter has been added and directs support for the newly added claims at various sections of the instant specification. However, the instant specification as filed does not provide sufficient written description for these "limitations".

Upon a review of the instant specification, it does not appear that the instant specification provides for written support for these above-mentioned "limitations". Applicant's reliance on generic disclosure and possibly the single species of the hu14.18 antibody that include a $V_L$ region as defined by SEQ ID NO: 1 and a $V_H$ region having at least one humanized FR, such as hu$V_H$FR1 or hu$V_H$FR2 does not provide sufficient direction and guidance to the antibody specificities, as well as the structural limitations, of "the antibody variable region of claim 1" and "further comprising an amino acid sequence selected from the group consisting of amino acids 1-25 of SEQ ID NO: 2 and amino acids 67-98 of SEQ ID NO: 2", as currently claimed.

It is noted that a generic or a sub-generic disclosure cannot support a species unless the species is specifically described. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

The specification does not provide sufficient blazemarks nor direction for the instant antibody encompassing the above-mentioned "limitations" as they are currently recited. The instant claim now recites limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Such limitations recited in the present claim, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the new matter in the response to this Office Action. Alternatively, applicant is invited to provide sufficient written support for the "limitations" indicated above. See MPEP 714.02 and 2163.06.

The amended claims 6-11, 17-19, 23-24 and 45-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1) an anti-GD2 antibody comprising both light chain and heavy chain variable regions, or 2) a fusion protein comprising said anti-GD2 antibody and a 1st or a 1st and 2nd moiety consisting of IL-2 and/or IL-12, that targets a cells with GD2 on its surface, does not reasonably provide enablement for 1) an antibody comprising fragments of variable regions, e. g. amino acids 1-23 of SEQ ID NO: 1, or 2) a fusion protein comprising an antibody variable region or fragment thereof, and a 1st or a 1st and 2nd moiety of any cytokine to target a cell with GD2 on its surface or to use as a therapeutic agent . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Applicant argues that the amended claims recite "[a]n antibody variable region comprising the amino acid sequence set forth in SEQ ID NO: 1" (claim 1), or "[a]n antibody variable region comprising the amino acid sequence set forth in SEQ ID NO: 2" (claim 2), or "[a]n antibody variable region comprising an amino acid sequence selected from the group consisting of amino acids 1-23 of SEQ ID NO: 1, amino acids 1-25 of SEQ ID NO: 2, and amino acids 67-98 of SEQ ID NO: 2" (claim 6). Therefore, one of

ordinary skill in the art would know how to make antibody constructs of the present invention.

Applicant's arguments have been fully considered but have not been found to be persuasive for reasons set forth in the 23 May 2005 Office Action.

As stated in the 23 May 2005 Office Action, Alberts et al. and do Couto et al. teach that both the light chain and heavy chain variable regions are generally required for the binding properties of the antibody. The instant claims read on using portions of the antigen binding domain. The specification, however, has provided no support for portions of the antigen binding domain which retains antigen binding property, i.e. binding to GD2. In fact, Okumura et al. (U. S. Patent 6,777,540 B1) teach a humanized immunoglobulin, wherein the variable region of the light chain comprising amino acid residues 1-23 of SEQ ID NO: 1 (100% identity to the instant antibody variable region as claimed), reacting specifically with FAS ligand.

In addition, claims 17-18 and 23 read on a fusion protein comprising a antibody variable region or fragment thereof, and a 1$^{st}$ or a 1$^{st}$ and 2$^{nd}$ moiety of any cytokine to target a cell with GD2 on its surface or to use as a therapeutic agent. While Applicant has shown that administration of hu14.18-IL-2 to cancer patients resulted in stabilization of disease progression by delivering IL-2 to GD-2 positive tumor cells and activating IL-2 responsive cells. Applicant, however, does not teach any cytokine which exhibits anti-tumor activity when conjugated to the antibody of the instant invention. Cytokines encompass a large family of proteins that exhibit different roles in the regulation of cell growth and differentiation in different tissues. For example, Demirci and Li (2004, Cell

Mol. Immunol., 1(2):123-128) teach that IL-2 and IL-15 exhibit opposite effects on Fas mediated apoptosis (pp. 123, Abstract), more specifically, IL-2 and IL-15 can have opposing effects on life and death of T cells.

Since the specification fails to provide guidance as to portions of antigen-binding domain or a fusion protein comprising said portions of antigen-binding domain to be able to bind GD2 on cell surface, and fails to provide guidance as to any cytokines, rather than IL-2 and IL-12, to have anti-tumor activity, which would be encompassed by the instant invention, the skilled artisan could not predictably identify such antibodies or fusion proteins, or such cytokines other than IL-2 and IL-12, nor could the artisan predictably use the antibodies or fusion proteins for therapeutic agents. The scope of patent protection sought by Applicant as defined by the claims fails to correlate reasonably with the scope of enabling disclosure set forth in the specification.

Due to the large quantity of experimentation necessary to determine what portions of antigen-binding domain or a fusion protein comprising said portions of antigen-binding domain to be able to bind GD2 on cell surface, and what cytokines, rather than IL-2 and IL-12, have the anti-tumor activity as the hu14.18-IL2, the lack of direction/guidance presented in the specification regarding such structure limitations for the function of the portions of antigen binding domain, and regarding any cytokines exhibiting IL-2-like function, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the complex of structure requirement for antigen-antibody interaction, and the diversity of mode of action for cytokines, and unpredictability of therapeutic outcomes, and the breadth of

the claims which read on any cytokines and portions of antigen binding fragment, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The amended claims 6-7, 10-11, and 48 are rejected under 35 U.S.C. 102(b) as being anticipated by Okumura et al. (U. S. Patent 6,777,540 B1). Okumura et al. teach a humanized immunoglobulin, wherein the variable region of the light chain comprising amino acid residues 1-23 of SEQ ID NO: 1 (see alignment). The humanized immunoglobulin of '540 Patent also comprising an Fc portion wherein the Fc portion comprising at least a CH2 domain and is derived from IgG1 (column 16, lines 13-27). Okumura et al. teach that the humanized immunoglobulin of '540 Patent can be used to treat HIV which expedites the expression of Fas ligand to induce apoptosis of the T cells expressing Fas antigen. Since applicant amended the claims to cancel functional limitations and only include the structural limitations, the '540 Patent thus meets the limitations of the amended claims 6-7, 10-11 and 48.

***Double Patenting***

The provisional double patenting rejection of claim 6, 17-19 and 23-24 over claims 1-5 and 13 of copending Application No. 11/040,071 remains in record as set forth in the previous office action (23 May 2005).

***Conclusion***

Claims 6-11, 17-19, 23-24 and 45-48 are rejected.

Claims 1-5 are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Xiaozhen Xie whose telephone number is 571-272-5569. The examiner can normally be reached on M-F, 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 571-272-0829. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Xiaozhen Xie, Ph.D.
December 9, 2005

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